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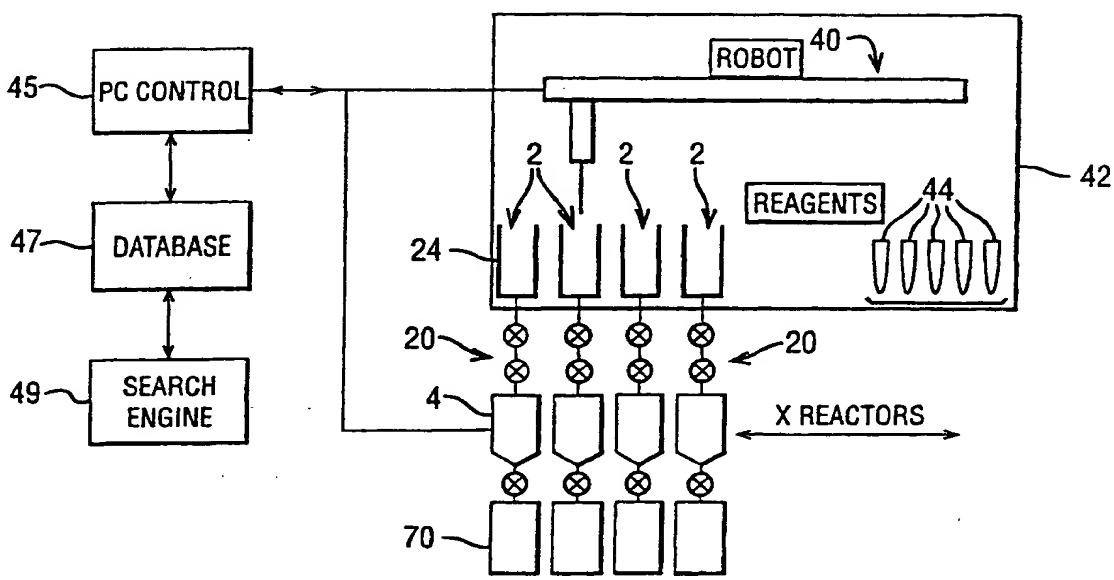

(57) Abstract: A system and method for examining chemical reactions, especially catalysed polymerisation reactions, uses an array of apparatuses (2) within a nitrogen filled glove box (42). A multi-pipetting robot (40) is arranged to deliver measured amounts of materials (e.g. catalyst components) to mixing vessels (24) which in turn are arranged to deliver the components to reactors (4) into which other components (e.g. monomer gases) are fed. A range of variables for reactions undertaken in apparatuses (2) are controlled by a computer (45) which also stores data relating to reactions effected in a database. A library of products can be made using the system under carefully controlled and reproducible conditions and parameters affecting the properties of products produced can be investigated.

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EXAMINING CHEMICAL REACTIONS

This invention relates to the examination of chemical reactions and particularly, although not exclusively, relates to the examination of reactions involving a catalyst system. Preferred embodiments relate to a method of examining the effect in a chemical reaction, for example an olefin polymerisation reaction, of varying selected variables and apparatus therefor.

Catalysts are widely used in polymerisation reactions. However, assessment of the effect and/or efficiency of catalysts and other variables in polymerisation reactions is extremely slow and time-consuming. It is an object of the present invention to address such problems.

According to a first aspect of the invention, there is provided a method of examining the effect in a chemical reaction of varying selected variables, the method comprising preparing a first product using a first set of experimental variables and preparing a second product using a second set of experimental variables, wherein data relating to said first and second sets is stored by an electronic data storage means, for example a computer.

The invention extends to a method of high-throughput screening of chemical reactions, the method comprising preparing a first product using a first set of experimental variables and preparing a second product using a second set of experimental variables, wherein data relating to said first and second sets is stored by an electronic data storage means, for example a computer.

The invention extends to a method of making a library of products, the method comprising varying experimental variables between chemical reactions in order to prepare a multiplicity of products, wherein data relating to experimental variables used for preparing each product is stored by an electronic data storage means, for example a computer.

The invention extends to a method of effecting automatically a multiplicity of chemical reactions, the method comprising preparing individual products using respective sets of experimental variables, wherein data relating to said sets is stored by an electronic data storage means, for example a computer and, preferably, the preparation of said products is computer controlled.

In general terms, the methods may be used in relation to any reactions in which one or more components need to be delivered at greater than ambient pressure, especially at relatively high pressures of up to 100 bar. Said one or more components may be reactive components, solvents and/or catalysts. Said one or more components may be gases, high pressure liquids (i.e. substances that act as liquids but which must be compressed and kept contained in order to remain a liquid, such as isobutane, ammonia, isobutylene and butene)and/or supercritical liquids.

The methods may be used in relation to hydrogenations, hydroformylations, reductions (e.g. hydrogen or liquid ammonia reductions), polymerisations, oligomerisations, carbonylations, isobutylene reactions and reactions involving carbon dioxide.

The methods may be used for optimising any type of reaction, for example a reaction involving the preparation of an active ingredient, for example a drug. Advantageously, the methods may be used in parallel exploration of scale-up reactions for preparation of active ingredients, suitably on a relatively large (g or Kg) scale.

Preferably, the reaction involves the use of a catalyst system and the method involves examining the effect of varying selected variables relating to said catalyst system.

The methods are suitably for measuring the effect of varying selected variables in a polymerisation reaction, wherein said first and second products (preferably a multiplicity of products prepared) are suitably polymers, prepared by polymerisation of one or more monomers in the presence of a catalyst system.

A reactor means is preferably provided in which said first and second products are prepared. Said reactor means suitably has a volume of at least 25 ml, preferably at least 50 ml, more preferably at least 75 ml, especially at least 100 ml. The volume suitably is less than 500 ml, preferably less than 300 ml, more preferably less than 200 ml, especially less than 150 ml. Said reactor means preferably includes an agitator means for agitating, for example by stirring, the contents of the reactor means. Means for varying the extent of agitation provided by the agitator means is preferably provided. One of the experimental variables in said first and second sets may be related to the extent of agitation. The method may,

therefore, include the step of varying the extent of agitation between at least two chemical reactions for examining the effect of varying the agitation on the chemical reaction under consideration. The method preferably includes storing data relating to the agitation, for example the stirring rate. Said extent of agitation is preferably controlled by a computer and more preferably is controlled by said computer which stores data relating to first and second sets of variables.

In one embodiment, the power supplied to a stirrer provided in the reactor means may be monitored and data relating thereto stored in the data storage means. Such data may give an indication on the viscosity of fluid in the reactor means during a reaction. For example, if the frequency of the stirrer is kept constant, the power supplied to the stirrer can give an indication of viscosity of the material being stirred.

The method preferably includes heating said reactor means. The method may include cooling said reactor means. Heating and/or cooling of said reactor means are preferably controlled by a computer, more preferably by said computer which stores data relating to said first and second sets of variables. The method preferably includes storing data relating to the temperature in said reactor means, during the chemical reaction.

The method preferably includes supplying via a first supply means one or more components for the reaction to the reactor means. Said supply is preferably controlled by a computer, more preferably by said computer which stores data relating to said first and second sets of variables.

Said computer preferably controls the opening and closing of a valve for controlling said supply. One, preferably a plurality, of the experimental variables in said first and second sets is related to the supply of said one or more components via said first supply means. The method preferably includes storing data relating to the supply of the said one or more components. The method may include storing data relating to (and/or experimental variables in said first and second sets may be based on) at least one, suitably at least two, preferably at least three, more preferably at least four, especially each of the following: the identity of said one or more components supplied; the timing of the supply of said component(s) in the context of the chemical reaction; the rate at which said one or more components is supplied; the pressure at which said one or more components is supplied; the total amount of each of said one or more components supplied in a chemical reaction.

Preferably, in the method, a first substance is supplied via said first supply means. Said first substance is preferably a reactant. Suitably, at least a part of said first substance is incorporated into a product produced in the reaction. Said substance may be a fluid, especially a gas. Where a polymer is prepared in the reaction, said first substance is preferably a monomer gas. Preferably, said monomer gas is an optionally-substituted olefin which term includes cyclic olefins and dienes. Examples of simple olefins include, for example ethylene, propylene, butene, pentene, heptene and octene, with propylene and especially ethylene being preferred. Examples of substituted olefins include vinyl compounds, for example styrene, acrylic acid, esters thereof and

acrylonitrile. An example of a cyclic olefin is norbornene. Examples of dienes include butadiene and isoprene. Said first substance may be supplied at a pressure up to 100 bar, preferably up to 50 bar, more preferably up to 30 bar. As aforesaid, the pressure of the supply of said first substance may be an experimental variable in the method. The pressure may vary between 1-100 bar, especially 1-30 bar.

Preferably, in the method, a plurality (preferably three or more) components for the reaction are supplied into a region, for example a receptacle or manifold, upstream of the reactor means and suitably caused to become mixed therein. Thereafter, the components can flow from the region into the reactor means. Advantageously, in this case, the method may be used when two components (especially fluids and/or gases) are used in the chemical reaction and, suitably, at least a part of each of said two components is incorporated into a product produced in the reaction. Where a polymer is prepared in the reaction, said two components may be reactants and may both be monomer gases, with ethylene and propylene being examples thereof. Other components may be supplied into said region. For example, a solvent, especially a high pressure liquid may be supplied. Also, a reaction intermediary (e.g. a chain transfer agent or the like) may be supplied.

The method may include assessing the amount of at least one (preferably a plurality) of said components for the reaction present in said reactor means at a plurality of intervals during a reaction in said reactor means. The method preferably includes sampling from the reactor means at intervals during a reaction. Preferably, fluids, for

example gases are sampled. The method may utilise any suitable means for assessing the amount(s) of said component(s). Mass spectroscopy is preferred, especially where the amounts of a plurality of components are assessed.

The method preferably includes supplying via a second supply means one or more components for the reaction to the reactor means. Said supply is preferably controlled by a computer, more preferably by said computer which stores data relating to said first and second sets of variables. Said computer preferably controls the opening and closing of valves for controlling said supply. One, preferably a plurality, of the experimental variables in the first and second sets is related to the supply of said one or more components via said second supply means. The method preferably includes storing data relating to the supply of said one or more components. The method may include storing data relating to (and/or experimental variables in said first and second sets may be based on) at least one, suitably at least two, preferably at least three, more preferably at least four, especially each of the following: the identity of said one or more components supplied; the timing of the supply of said component(s) in the context of the chemical reaction; the order of supply of said component(s); the rate at which said one or more components is supplied; the pressure at which said one or more components is supplied; and the total amount of each of said one or more components supplied in a chemical reaction.

The order of supply of components into the reactor via said first and second supply means may be an experimental

variable included within said first and second sets and/or data relating to the order may be stored.

Preferably, in the method, a second substance is supplied via said second supply means. Said second substance could be a substrate, monomer, anti-static agent, chain termination agent or inert filler. Said second substance may comprise a catalyst system or a component of a catalyst system. Suitably, a said catalyst system is arranged to catalyse a reaction, suitably involving a first substance which may be supplied via said first supply means and/or could be supplied via said second supply means. Optional further substances may be supplied via said second supply means.

At least 0.1 μg, preferably at least 0.5 μg, more preferably at least 0.75 μg, especially at least 1 μg of said second substance may be supplied. The amount of said second substance may be less than 5000 μg, preferably less than 3000 μg, more preferably less than 1500 μg, especially 1000 μg or less. The aforementioned amounts suitably relate to the weight of active material, not including any support therefor. The amount of said second substance may be an experimental variable included within said first and second sets and/or data relating to said amount may be stored. The amount of catalyst may be varied within wide limits, suitably up to a stoichiometric amount relative to other reactants involved in the reaction.

The method preferably includes injecting said second substance and one or more optional further substances into

the reactor means, suitably under pressure, which is preferably predetermined. The injection is preferably controlled by a computer, more preferably by said computer which stores data relating to said first and second sets of variables. Said computer preferably controls the opening and closing of valves for controlling said injection. To this end, upstream of the reactor means, there is suitably provided a fluid reservoir means for receiving material, for example, fluid (e.g. liquid) to be injected in the reactor means. The method preferably includes generating pressure in the fluid reservoir means. The fluid reservoir means suitably has a volume of at least 2ml, preferably at least 3ml, more preferably at least 4ml. The volume may be less than 50ml, suitably less than 30ml, preferably less than 20ml, more preferably less than 10ml, especially 6ml or less. Suitably, in the method, at least 40%, preferably at least 60%, especially at least 80%, of the volume of the reservoir means is filled with a non-gaseous material for injection into the reactor means. Said reservoir means may have a volume up to 20% of the volume of the reactor means.

The method may include delivering a fluid, especially a gas, for example an inert gas such as nitrogen or argon, under pressure into the fluid reservoir means. The method preferably includes pressurising the fluid reservoir means and then causing the contents thereof to be injected into the reactor means. Preferably, a computer, more preferably said computer which stores data relating to said first and second sets of variables causes said injection, suitably by opening and/or closing valves.

A catalyst system or a component of said catalyst system supplied via said second supply means may be prepared in the method. Alternatively, a pre-prepared catalyst system or component may be supplied via said second supply means. Where a catalyst system or component is prepared in the method,the method preferably includes storing data relating to the preparation of said catalyst system and/or a component thereof. The catalyst system and/or a component thereof may be oxygen and/or moisture sensitive and, accordingly, its preparation and/or storage is preferably carried out substantially in the absence of oxygen and/or moisture. Preferably, the preparation is carried out in an inert atmosphere, for example a nitrogen or helium atmosphere or, especially, an argon atmosphere. Preferably, the preparation is carried out in an inert gas-filled environment, for example a glove box. Said catalyst system or a component thereof may be prepared by contacting a first catalyst component with a second catalyst component and, optionally, with other catalyst components. The preparation is preferably computer controlled, more preferably by said computer which stores data relating to said first and second sets of variables. The method preferably includes storing data relating to (and/or experimental variables in said first and second sets may be based on) at least one, suitably at least two, preferably at least three, especially each of the following: the identity of said first catalyst component; timing of the supply of said first catalyst component; the order of the supply of said first catalyst component relative to other components of the catalyst system; and the amount of said first catalyst component added.

The method preferably includes storing data relating to (and/or experimental variables in said first and second sets may be based on) at least one, suitably at least two, preferably at least three, especially each of the following: the identity of said second catalyst component; the timing of the supply of said second catalyst component; the order of supply of said second catalyst component relative to other components of said catalyst system; and the amount of said second catalyst component added.

Where the catalyst system includes other catalyst components, data relating to such components may be stored as described above for said first and second catalyst components.

The method may include preparing said catalyst system or a component thereof upstream of a reactor means in which products of the chemical reaction are prepared. Where the method includes injecting said catalyst system or a component thereof from a fluid reservoir means into the reactor means, preferably the method includes preparing said catalyst system or a component thereof upstream of the fluid reservoir means. The method may include preparing the catalyst system or components thereof in a preparation receptacle.

Said catalyst system may be for any type of chemical reaction, for example a hydrogenation reaction or any other reaction described herein. Preferably, however, it catalyses a polymerisation reaction, suitably for preparation of an organic polymer. It may polymerise the polymerisation of vinylacetate. Said catalyst system is

suitably for preparation of polyolefins and preferably catalyses the polymerisation of α-olefins which may be selected from ethylene, propylene, butene, pentene, heptene and octene. The method may be adapted to polymerise mixtures of polyolefins. Preferred α-olefins are ethylene and/or propylene. The use of such olefins can lead to the formation of crystalline polyethylene homopolymers and copolymers of both low and high density (HDPE, LDPE, LLDPE etc) and polypropylene homopolymers and copolymers (PP and EMPP). The catalyst system may also be used in the preparation of amorphous or elastomeric copolymers based on ethylene and another α-olefin. Propylene may be used as the other α-olefin, so that EPM elastomer is formed. A diene could be used besides ethylene and the other α-olefin, so that so-called EADM elastomer is formed, in particular EPDM (ethylene propylene diene) elastomer. An ethylene-norbornene elastomer could also be formed. The monomers needed for such products and the processes to be used are known to those skilled in the art.

Said catalyst system may be any type of catalyst system that it is desired to assess. However, it may be a highly sensitive catalyst system which is unstable in an oxygen and/or moist atmosphere. The catalyst may be inorganic. It may be a metallocene. The catalyst system may be as described in US 5646322 (DSM), EP 0427 697 (Fina) or EP 0420436 (Exxon) and the contents of the aforementioned documents are incorporation therein by reference.

In the method, a robot, especially a multi-pipetting, x, y, z robot, suitably delivers components for said chemical reaction. Preferably, said robot is involved in the preparation of said catalyst system or a component thereof, for example the contacting of a said first catalyst component with a said second catalyst component. Preferably, said robot delivers said first and second catalyst components to a place where they are contacted. Where the catalyst system or a component thereof is prepared in a preparation receptacle, preferably said robot delivers said first and second catalyst components to said receptacle. Said robot is preferably arranged to deliver predetermined, optionally variable, amounts of components. Said robot is preferably controlled by a computer and, more preferably, is controlled by said computer which stores data relating to said first and second sets of variables. It will be appreciated that the preparation of said catalyst system or a component thereof is suitably automatically executed under computer control.

Suitably, a said chemical reaction which takes place in said reactor means and is examined in the method is carried out for less than 3 hours, preferably less than $2^1/_2$ hours, more preferably less than 2 hours, especially less than 1 hour. Where a solution polymerisation is effected, the reaction could be 1 hour or less and is, suitably, about ½ hour. Where a slurry polymerisation is effected, the reaction could be longer, for example between ½ hour and 2 hours.

After termination of a chemical reaction, the product produced may be removed from the apparatus preferably automatically, under the control of a computer which

suitably controls operation of a valve associated with an outlet of the reactor means. Suitably, a fluid path is defined between the reactor means and a collection vessel. A robot, or other means, may be provided for removing, preferably automatically, the collection vessel from said fluid path after a reaction and replacing the removed vessel so as to collect a subsequent product prepared in the apparatus. After collection of a product, it may be analysed, for example by GPC and by other techniques and data relating to the analysis is input into the electronic data storage means, suitably said computer.

In a preferred embodiment, said collection vessel is a component of a collection assembly which is preferably disengaged from a said reactor means in the method. The method preferably involves a robot twisting the collection assembly about a first axis and, suitably, moving the assembly in a direction parallel to said first axis. The method may include a robot disengaging said collection vessel (suitably containing a reaction product) from the collection assembly and placing the collection vessel in a predetermined location. The method may include replacing the removed collection vessel with another collection vessel. Thereafter, the method may include re-engaging the collection assembly with the reactor means.

The method preferably includes cleaning the reactor after a reaction has been undertaken. Such cleaning is preferably carried out automatically, suitably according to a predetermined procedure, preferably under control of a computer.

Advantageously, sufficient data is stored relating to each chemical reaction undertaken to enable chemical reactions to be reproduced to produce substantially identical products, under computer control.

Selection of values for variables in said first and second sets may be under operator control. However, additionally, or alternatively, selection of variables may be under computer control. In this case, variables may be adjusted in dependence upon assessments made with respect to earlier reactions.

The method suitably includes analysing the data relating to said first and second sets of variables and determining the effect of individual variables on the chemical reactions and/or characteristics of products produced.

The method may involve undertaking at least 5, suitably at least 10, preferably at least 15, more preferably at least 20, especially at least 40, separate reactions to prepare products using experimental variables as described. Data relating to all of the reactions may be stored for analysis. Advantageously, because reactions can be carried out relatively rapidly, with a high level of automation, more than 15 reactions may be carried out using a single apparatus arranged to carry out the methods described in a day. In fact, because of the high level of automation, the apparatus can be left unattended overnight.

When the method is used to screen a new catalyst 5-10 reactions may be undertaken. Where the method is used to

optimize variables, thousands of reactions may be undertaken. It will be appreciated that the automated system described makes it relatively easy to undertake large numbers of reactions.

A plurality, suitably at least 2, preferably at least 4, more preferably at least 6, especially at least 8, apparatuses (which are preferably substantially identical), may be provided, each of which is arranged to carry out the methods described, suitably in parallel. Thus, said first product described may be prepared by an apparatus and said second product may be prepared by the same or another apparatus. Said plurality of apparatuses may be served by the same robot and may be provided in, or associated with, the same inert gas-filled environment. Furthermore, they may be controlled by the same computer. Thus, advantageously, a single computer may be used to control, independently, the execution of the methods described in each apparatus; and, preferably data collated is stored by the same computer.

Where the methods described are undertaken in parallel using a plurality of apparatus, at least one, suitably at least two, preferably at least three, more preferably at least four, especially at least five of the following variables may be selected for one apparatus independently of another (preferably each other) apparatus:

- the extent of agitation in said reactor means;
- the temperature in said reactor means;
- the pressure at which one or more components is supplied to the reactor means;
- the rate at which said one or more components is supplied to the reactor means;

- the total amount of one component supplied to the reactor means for a chemical reaction;
- the total amount of another component supplied to the reactor means for a chemical reaction;
- the ratio of the amount of one component supplied to the reactor means relative to the amount of another component supplied to the reactor means;
- the duration of a chemical reaction.

Where the method involves assessing the amount of at least one of said components for the reaction present in said reactor means, and where a plurality of reactor means is used, a single means (e.g. a single mass spectrometer) may be used to asses the amounts of said components.

The invention extends to a system which includes apparatus for carrying out any of the methods described herein.

The invention extends to a system for examining the effect of adjusting selected variables in a chemical reaction, the system comprising an apparatus which includes:

a reactor means;

a first supply means for supplying a first substance to the reactor means;

a second supply means for supplying one or more components for the chemical reaction to the reactor means;

wherein said system includes electronic data storage means, for example a computer, associated with the apparatus for storing sets of variables relating to separate reactions undertaken using the apparatus.

Said reactor means is preferably an autoclave. It is preferably operable at a pressure up to 100 bar and a temperature up to 200°C. Means for heating said reactor means is preferably provided. Means for cooling said reactor means is preferably provided. Means for measuring temperature associated with the reactor means is preferably provided. The apparatus is preferably such that data relating to temperature is relayed to said computer. Said computer preferably controls the heating and/or cooling of the reactor means.

Agitator means is preferably provided in said reactor means. The apparatus is preferably such that data relating to agitation effected by said agitation means is relayed to said computer. Said computer preferably controls said agitator means.

Said first supply means is preferably arranged for the supply of a fluid, especially a gas, preferably under pressure, to said reactor means. Valve means is preferably provided for controlling supply of fluid to said reactor means via said first supply means wherein operation of said valve means is arranged to be controlled by said computer. Means is preferably provided for measuring the amount of fluid passing to said reactor means via said first supply means. The apparatus is preferably such that data relating to said amount is relayed to said computer.

Means may be provided for removing water from fluid prior to passage into the reactor means via said first supply means. Means may be provided for analysing the level of oxygen and/or water in such fluid. The computer may be arranged to control valves to allow gas to flow to an area where it may be automatically analysed.

Means may be provided for supplying two gases, preferably three gases, into the reactor means via said first supply means. In one embodiment, the apparatus may include a receptacle (e.g. a manifold), upstream of the reactor means, wherein said receptacle includes a plurality of gas inlets and said receptacle is arranged for supply of gases from the receptacle into the reactor means via said first supply means.

The apparatus may include a sampling means for withdrawing a fluid (especially a gas) sample from the reactor means and, suitably, directing the sample withdrawn to a remote location for analysis. Preferably, said sampling means extends out of the reactor means via said first supply means. An internal region of said sampling means is, however, suitably isolated from fluids passing into the reaction means via said first supply means. Preferably, an inlet end of said sampling means extends further into the reactor means than an outlet end of the first supply means via which fluids flow into the reactor means. Said inlet end of said sampling means is preferably turned away from said outlet end of the first supply means so that the sampling means receives a representative sample from within the reactor means.

Said system may include means (e.g. a mass spectrometer) for analysing fluid (especially gas) samples withdrawn from said reactor means.

Said second supply means is preferably arranged for the supply of a fluid, especially a liquid, to said reactor means. Means is preferably provided for injecting fluid, under pressure, into said reactor means, suitably against the pressure present in the reactor means. Said means for injecting fluid may include a fluid reservoir means for containing fluid to be injected and means for pressurising the fluid, such means suitably including a gas supply. Thus, preferably, said fluid reservoir means includes a fluid supply line for input of a pressurising gas. The computer is preferably arranged to initiate injection of the fluid into the reactor means. To this end, the computer may be arranged to operate valve means positioned between the reactor means and fluid reservoir means whereby injection takes place when the valve means is operated. The computer may also control operation of a valve upstream of the fluid reservoir means.

The apparatus preferably includes means for removing water from the pressurising gas prior to its passage into the reactor means. Means may be provided for analysing the level of oxygen and/or water in said pressurising gas. The computer may be arranged to control operation of valve means to allow pressurising gas to flow to an area where it may be automatically analysed.

The apparatus preferably includes a preparation receptacle for supplying catalyst(s) (or fluids or solutions or substrate solutions) to the reactor. Said

receptacle is preferably upstream of the fluid reservoir means and, suitably, a valve means is arranged between the two, which valve means is suitably arranged to be controlled by the computer.

Said preparation receptacle is preferably arranged in an inert environment. For example, it may be arranged in an inert-gas filled cabinet. Said receptacle is preferably arranged to receive material dispensed by a robot, suitably positioned within the inert environment. Agitation means is preferably associated with said receptacle.

Said system preferably includes said robot which is suitably controlled by said computer. It is preferably arranged to transfer predetermined amounts of materials from storage positions, suitably within the inert environment, into the apparatus, preferably into the preparation receptacle thereof.

A valve means is preferably associated with an outlet of the reactor means for controlling removal of product from the reactor means. A fluid flow path is preferably defined between the reactor means and a collection vessel. Said valve means is preferably computer controlled.

Said collection vessel is preferably a component of a collection assembly which is releasably secured relative to the reactor means. Said collection vessel is preferably disengageable from the collection assembly. Said system preferably includes a robot for releasably securing the collection assembly in position and for disengaging the collection vessel from the collection assembly.

Said system preferably includes a plurality of apparatuses of the type described. Each apparatus in said system is preferably substantially identical. Catalyst preparation receptacles of the apparatuses are preferably provided in the same inert environment. Said robot is preferably arranged to deliver materials into each apparatus under the control of the computer. Preferably, a single computer is provided for communicating information to and receiving information from the plurality of apparatuses. Preferably, said single computer is arranged to control operation of valves means of the apparatuses.

The invention extends to the use of a system of the type described in examining the effect of adjusting selected variables in a chemical reaction.

The invention extends to the use of a system of the type described in high-throughput screening of chemical reactions.

The invention extends to the use of a system of the type described in making a library of products.

The invention extends to a library of products in combination with a database incorporating data for each product, wherein said data relates to experimental variables used for preparing each product.

The invention extends to the use of a system of the type described in effecting automatically a multiplicity

of chemical reactions which differ in at least one experimental variable.

The form of automatic control described herein may be applicable not only to the polymerisation reaction focussed on but to any hydrogenation, carbonylation, carboxylation, carboxyalkylation, reduction, oxidation or halogenation reaction. All chemicals, temperatures, pressures, gas evolution, gas consumption etc. can be subject to variation in the course of a chemical process and thus monitoring, control and feedback on variables measured and/or detected allows controlled predictability of the next desired set of variables in an experimental set.

Any feature of any aspect of any invention or embodiment described herein may be combined with any feature of any aspect of any other invention or embodiment described herein.

Specific embodiments of the invention will now be described, by way of example, with reference to the accompanying drawings, in which:

Figure 1 is a schematic representation of apparatus for preparing a polymer;

Figure 2 is a schematic representation of an array of apparatuses for preparing polymers;

Figure 3 is a schematic representation of apparatus for preparing a polymer (provided on three separate sheets);

Figure 4 is a modified version of the apparatus of figure 1;

Figure 5 is a schematic representation of a set-up for sampling from an array of apparatuses of the type shown in figure 4 and analysing samples by mass spectroscopy;

Figure 6 is a cross-section through a dumping assembly;

Figure 7 is a cross-section along line VII-VII through a housing for a dump vessel (with the dump vessel itself omitted in the interests of clarity).

In the figures, the same or similar parts are annotated with the same reference numerals.

Whilst the apparatus is described hereinafter with reference to the preparation of polyethylene, this is only one example of a reaction that may be undertaken. The apparatus may be used for a very wide range of reactions.

In one embodiment, the apparatus may be used in the preparation of polyethylene polymer using ethylene gas, a catalyst and an optional co-catalyst in the presence of an inert solvent, for example pentamethyl heptane (PMH). The apparatus allows the preparation of the polymer under variable but highly controlled, monitored and/or reproducible conditions.

General features of the apparatus are shown in figure 1. The apparatus 2 includes a reactor vessel 4, which is

surrounded by an electrical heating means 6 and a water-cooling means 8. A stirrer 10 extends into the vessel and is driven by a motor 12. A monomer input line 14 is arranged for passage of ethylene monomer into the vessel, with the pressure of the monomer being monitored by pressure gauge 16. A second input line 18 communicates with the vessel 4 for delivery of reagent(s)/solvent(s) thereinto. Upstream of the line 18, there is provided an injection chamber 20 for receiving reagent(s)/solvent(s) prior to pressurised injection thereof into the vessel 4. The injection chamber 20 communicates with a nitrogen gas supply line 22. A premixing vessel 24 which includes a stirrer (not shown) is arranged upstream of the injection chamber 20 for delivering reagent(s)/solvent(s) thereinto. The premixing vessel is enclosed in a nitrogen-filled glove box. Various valves (not shown) are provided for controlling passage of fluids through the apparatus.

In brief, the apparatus may be used as follows. With the stirrer 10 and heating means 8 actuated and PMH (supplied via line 18) saturated with ethylene (supplied via line 14) being present in the vessel 4, a catalyst is prepared in pre-mixing vessel 24 by contact of a ligand and transition metal in the presence of PMH and a co-catalyst is optionally added to the mixture. The mixture is allowed to pass into injection chamber 20 where it is pressurised by nitrogen gas and injected under pressure into vessel 4 wherein an ethylene polymerisation reaction takes place. During this time, ethylene is continuously supplied into vessel 4 to maintain ethylene saturation. After a time, the reaction is stopped and the polymer prepared is collected and analysed.

In a preferred embodiment, represented schematically in figure 2, an array, for example having eight members (only four of which are shown in the figure), of apparatuses 2 are arranged side by side, with their pre-mixing vessels 24 being arranged in a nitrogen filled glove box 42 (< 1ppm H_2O; <1 ppm O_2 atmosphere). A multi-pipetting robot 40 (an X, Y, Z gantry system type)is positioned in the glove box and is arranged to deliver measured amounts of materials (e.g catalyst components, co-catalyst(s), solvent(s) etc.) from vessels 44 into respective pre-mixing vessels 24. The catalyst components and/or the catalyst may be air and/or moisture sensitive organometallic complexes, hence the need for the nitrogen atmosphere. The vessels 4 of the apparatuses 2 may have a volume of 125ml and be electrically heated and cooled by water. Each can independently run polymerisations of ethylene at up to 100 bar and at temperatures in the range of 50-150°C. The robot 40 and the apparatuses 2 are under the control of a single computer 45 which also stores data relating to reactions effected in a database 47, wherein a search engine 49 is provided for searching the database.

A more detailed representation of apparatus is provided in Figure 3. Whilst eight apparatuses 2 are suitably provided, with their respective pre-mixing vessels 24 and a solvent supply 50 arranged within the glove box (the floor 52 of which is represented), only one apparatus 2 is shown in the figure. Other components of the apparatus are provided outside the glove box because they are, in any event, effectively sealed from the surrounding atmosphere.

The apparatus of Figure 3 may be used according to the following description.

Initially, the atmosphere in the glove box is tested to ensure that it contains less than 1ppm H_2O and less than 1ppm oxygen gas. Then, before starting a polymerisation experiment, reactor vessel 4 is rinsed, according to a predetermined regime, with the robot delivering suitable solvents, and the computer controlling the opening and closing of valves and operation of heaters.

Upstream of the apparatus 2, ethylene cylinders 90 are provided and arranged to deliver gas at up to 100 bar, via drying columns 92a, Brooks (Trade Mark) flow controller 60 and input line 14, to the reactor vessel 4. (The Brooks flow controller is a mass flow controller. It controls the maximum flow rate of gas in gas lines with which it is associated and the amount, both in terms of the instaneous amount flowing and the total amount delivered). The gas may be diverted for analysis to respective oxygen and water analysis circuits 94a, 96a. Flow of ethylene gas is controlled by valves labelled 98ET, 98F and valve 62 which are, in turn, operated by the computer.

Upstream of the apparatus 2, nitrogen cylinders 110 are provided and arranged to deliver gas, via drying columns 92c, at a pressure in the range 1 - 100 bar, preferably at about 30 bar, into supply line 22. The gas may be diverted for analysis to respective oxygen and water analysis circuits 94a, 96a. Flow of nitrogen is controlled by valves labelled 98N, 98F and 66 which are, in turn, operated by the computer.

Solvent is supplied to vessel 50 from a vessel 100 via drying columns 92d and, optionally, via a water analyser 102.

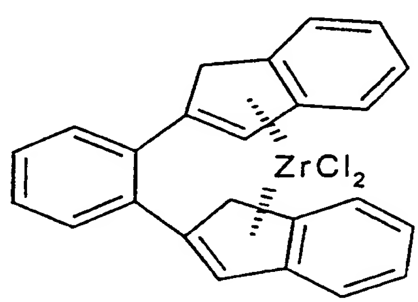
Another gas may be input into the ethylene stream, if desired. For example, hydrogen gas may be added to the stream to act as a chain transfer agent and/or to control molecular weight. The facility for inputting another gas includes gas cylinders 104 which are arranged to deliver gas, via drying columns 92b, Brooks flow controller 60 and input line 14, to the reactor. The gas may be diverted for analysis to respective oxygen and water analysis circuits 94a, 96a. Flow of the gas is controlled by valves labelled 98G, 98F and 63 which are, in turn, operated by the computer.

The polymerisation procedure is executed automatically by the robot under control of the computer. The procedure is as follows:

Firstly, the reactor vessel is loaded and saturated with ethylene. In this regard, PMH (70ml), together with a predetermined amount of scavenger (or co-monomer), are added to pre-mixing vessel 24 by the robot. Then the temperature of the reactor vessel 4 is set 20°C below a predetermined set point and the procedure is discontinued until the set temperature is reached. The contents of the vessel 24 are added to the reactor vessel 4 by opening valves 54, 56 and 58. After waiting a few seconds, valves 54, 56, 58 are closed and stirrer 10 is turned on. Brooks flow meter 60 is opened and its totalizer re-set to zero and then valve 62 is opened thereby to pressurise the

reactor 4 with ethylene. After a few seconds valve 62 is closed and the reactor temperature is then set 10°C below its set-point and the procedure discontinued until the set temperature is reached. Once the set temperature is reached, the Brooks flow meter 60 is opened totally and its totalizer reset. Then, by opening valve 62 the reactor vessel is pressurised to 20 bars of ethylene and the temperature rises to the set point. The gas saturation of the reactor vessel is thereby complete and the subsequent procedure will not continue until the flow as measured by the Brooks flow meter equals zero and the temperature equals the set-point.

Next, reagents are injected under pressure into the reactor vessel. (The catalyst used may be



which may be prepared in the glovebox as a 0.0001M solution in toluene. A co-catalyst may be MAO). In this regard, PMH, catalyst (and optionally co-catalyst) are added to the pre-mixing vessel 24 by the robot in a predetermined procedure (hereinafter referred to as the "charging PID") which may suitably include stirring it and the mixture is mixed according to a predetermined procedure (hereinafter referred to as the "mixing PID") for 1 minute before valves 58 and 64 are opened to introduce it into the injection chamber 20. After several seconds valves 58 and 64 are closed and valve 66

is opened for several seconds and then re-closed to pressurise the catalyst injection chamber 20. The Brooks flow meter 60 is opened totally and its totalizer reset to zero. At this stage 7.5 ml of PMH will already have been added to the pre-mixing vessel 24 for a second injection (whereby any remaining catalyst can be washed out of the vessel). Then, the first injection into the reactor vessel 4 takes place by opening and closing valve 56. After the first injection, the PMH for the second injection is introduced into injection chamber 20 by opening valves 58 and 64. After several seconds, valves 58 and 64 are closed and valve 66 is opened for several seconds (and closed again) to pressurise the injection chamber 20. The second injection into the chamber takes place by opening and closing valve 56.

While the polymerisation is ongoing, 100 ml of PMH for a first cleaning step of the apparatus is added by the robot to the pre-mixing vessel 24.

When the polymerisation has finished or after 30 minutes (whichever comes first), valve 62 is closed, thereby to shut off the ethylene supply, and the stirrer 10 is switched off. The polymer is collected in collection vessel 70 by opening drain valve 72 and, thereafter, it is re-closed. The collection vessel can then be disconnected from the apparatus and the polymer isolated. This may be undertaken automatically by a robot which may re-connect a clean collection vessel for collecting a polymer prepared in a subsequent reaction.

The computer then controls the cleaning of the apparatus and its preparation for another polymerisation reaction according to predetermined procedures.

During use of the apparatus, the temperature at predetermined locations, for example, the lid and body of the reactor, are monitored and controlled and data relating thereto is stored by the computer.

The apparatus also includes various alarm procedures including, for example, pressure and temperature alarms, which relay information to the computer which, in turn, controls safely measures taken (e.g. closing/opening of valves, switching off heaters etc,) in the event that an alarm is actuated.

The computer is arranged for input of a substantial amount of data relating to each polymerisation. There are two main types of data input: firstly, data describing general procedures used; and, secondly, data relating to experimental variables.

The following data describing general procedures may be input. In the following tables which describe data types, the first column is a short form description of the data; the second column describes the type of data (e.g. number or character); and the third gives a more detailed description of the data.

Table 1

Column Name	Type	Description
CLEANING PID	NUMBER	The identifier that specifies the procedure used to clean the reactor vessel
PREPARATION PID	NUMBER	The identifier that specifies the procedure used to prepare the reactor vessel
INITIAL DRYING PID	NUMBER	The identifier that specifies the procedure used to dry the reactor vessel
CHARGING PID	NUMBER	The identifier that specifies the procedure used to charge the pre-mixing vessel
MIXING PID	NUMBER	The identifier that specifies the procedure used to mix the reactants in the pre-mixing vessel
REACTION PID	NUMBER	The identifier that specifies the procedure used to clean the reactor vessel
DUMPING PID	NUMBER	The identifier that specifies the procedure used to clean the collection vessel

The following data describing procedural variables may be input.

Table 2

Column Name	Type	Description
REACTOR TEMPERATURE	NUMBER	The temperature in degrees centigrade of the body of the reactor vessel at the injection of the mixture as measured by a thermocouple
STIRRING RATE	NUMBER	The stirring rate (RPM) of stirrer 10 in the reactor vessel
NITROGEN PRESSURE	NUMBER	The supply pressure of Nitrogen (kPa) to line 22
ETHYLENE PRESSURE	NUMBER	The supply pressure of Ethylene (kPa) to line 14
DURATION OF EXPERIMENT	NUMBER	The experiment duration (seconds)

Procedures undertaken in the apparatus are divided into a series of numbered stages and a table is constructed specifying what procedure (e.g. opening/ closing particular valves, raising temperature, inputting components etc.) is undertaken at each stage. Also, where more than one procedure is undertaken at the same stage (e.g input of two components into a reaction), details relating to the order of such a procedure is noted. This enables any procedure to be reproduced.

The primary catalyst used in an experiment is referenced by identifying characters and various data relating thereto is stored, as follows:

Table 3

Column Name	Type	Description
PRIMARY CATALYST ID	VARCHAR2	The identifier for the sample of primary catalyst.
PRIMARY CATALYST VOLUME	NUMBER	The volume of primary catalyst added to the vessel (ml)
PRIMARY CATALYST MASS ADDED	NUMBER	The computed weight of primary catalyst added (g)
PRIMARY CATALYST MOL ADDED	NUMBER	The computed amount of primary catalyst added (mol)
PRIMARY CATALYST STAGE ADDED	NUMBER	The stage number in which the primary catalyst was added to the apparatus
PRIMARY CATALYST STAGE ORDER	NUMBER	The order within the set of reagents added at the same time as the primary catalyst

Other catalysts or co-catalysts may be added and these are identified as co-catalysts A to G giving eight potential co-catalysts. Data relating to co-catalyst A may be as follows. Data relating to co-catalysts B to G may be presented and stored in a similar manner.

Table 4

Column Name	Type	Description
CATALYST A ID	VARCHAR2	The identifier for the sample of co-catalyst A
CATALYST A VOLUME	NUMBER	The volume of co-catalyst A added to the vessel (ml)
CATALYST A MASS ADDED	NUMBER	The computed weight of co-catalyst A added (g)
CATALYST A MOL ADDED	NUMBER	The computed amount of co-catalyst A added (mol)
CATALYST A STAGE ADDED	NUMBER	The stage number in which the co-catalyst A was added to the apparatus
CATALYST A STAGE ORDER	NUMBER	The order within the set of reagents added at the same time as the co-catalyst A

The solvent in which experiments are undertaken provides another set of important experimental variables. Of primary interest are the solvent type and quantity and of secondary interest, to be used mainly for quality assurance, is the exact batch of solvent involved. As with catalysts/co-catalysts, it is important to know exactly when the solvent was added and what was added at the same time.

One or more solvents identified as solvents 1 to 8 may be added. Data relating to solvent 1 may be as follows. Data relating to solvents 2 to 8 may be presented in a similar manner.

Table 5

Column Name	Type	Description
SOLVENT 1 NAME	VARCHAR2	Name of the first solvent.
SOLVENT 1 SUPPLIER	VARCHAR2	Supplier identifier
SOLVENT 1 BATCH ID	VARCHAR2	Supplier batch identifier
SOLVENT 1 STAGE NUMBER	NUMBER	Stage number solvent 1 is added
SOLVENT 1 ORDER NUMBER	NUMBER	Order within the solvents added in this stage

Additionally, various parameters are measured during experiments, for example gas consumption and temperature change and data is stored. Temperature or gas traces are difficult to compare computationally and, accordingly, summary figures are prepared for use in analysis, as follows:

Table 6

Column Name	Type	Description
TEMP TOTAL RISE	NUMBER	The temperature rise in the body of the reactor vessel between the start and end of the experiment (°C)
TEMP MAX RATE	NUMBER	The maximum temperature rise rate over a 10 second period (°C)
FLOW TOTAL USED	NUMBER	The value on the totalizer at the end of the experiment (dm^3) thereby providing the total ethylene used
FLOW MAX RATE	NUMBER	The maximum amount of ethylene used in a 10 second period (dm^3)
FLOW TIME TO HALF MAX	NUMBER	The time taken to reach half the maximum flow rate (seconds)

The actual traces are stored as values vs time for temperature, pressure, ethylene consumed and % ethylene consumption.

After a polymer has been dumped in vessel 70 it may be taken away and analysed. Analytical information can also be input into the computer, for example, as follows:

Table 7

Column Name	Type	Description
EXPERIMENT ID	NUMBER	Primary key references the experiment table.
WEIGHT	NUMBER	Weight of a sample produced (g)
GPC MODE WEIGHT	NUMBER	Mode molecular weight of sample from GPC
GPC POLYDISPERSITY	NUMBER	Polydispersity of GPC sample
GPC FILE NAME	VARCHAR2	Name of GPC file
GPC ARCHIVE	VARCHAR2	Location of file archive

Additionally, structural information relating to catalysts/co-catalysts used can be input.

The stored data described above may be held within an Oracle (Trade Mark) table. Proprietary software sold under the Trade Mark RS^3 by Oxford Molecular Group Plc enables the data to be statistically analysed and searched.

The apparatus 200 of figure 4 differs from the apparatus 2 of figure 1 in that the apparatus 200 is adapted to allow more gas types to be input into the reactor vessel 4. To this end, a manifold 202 is provided upstream of the vessel 4. The manifold includes five gas inlets 204, 206, 208, 210 and 212 which, in an example, may be connected to supplies of ethylene (monomer gas), nitrogen (inert gas), propylene (monomer gas), hydrogen (chain transfer gas) and isobutane (solvent gas) respectively. The manifold communicates with the vessel 4 via inlet line 214.

The amounts of the five respective gases fed into the vessel 4 are controlled by respective mass flow controllers which also control the rate of gas feed. The mass flow controllers are controlled by a reactor control box 100 (figure 5) which sets the flow rates and the amounts of gases fed into the reactor. Each control box 100 communicates with a single central computer.

Since each reactant gas (e.g. ethylene, propylene, hydrogen) may be consumed at a different rate, the rates of flow are controlled independently, according to the composition of each gas in the reaction at points in time. To this end, the apparatus 200 includes a sampling capillary line 220 which passes through the manifold 202 and into the vessel 4. The line 220 is adapted to sample the gas in the vessel 4 and deliver samples to a mass spectrometer 102 (figure 5) which analyses it and delivers data relating thereto to the control box 100 which resets the mass flow controllers to make up for any differences in reaction rate and feed rate to thereby maintain a constant composition in the vessel 4. The capillary line 220 is heated so that gases therein do not separate based on their relative molecular weights.

As described above, an array of reactor vessels 4 is suitably provided. Each may incorporate a capillary line 220 as described above. However, one mass spectrometer may be used to analyse samples taken from the entire array of vessels 4. In this regard, an eight way switching valve 110 is arranged to allow sampling from one respective reactor at a time and, depending upon which rector 4 is being sampled, the mass spectrometer communicates relevant data to the appropriate control box 100.

In view of the modifications incorporated in the apparatus of Figure 4, additional variables may be stored and/or controlled by the computer, as follows:

Re: Table 2	-	propylene pressure;
	-	hydrogen pressure.
Re: Table 6	-	flow total for propylene;
	-	flow total for hydrogen;
	-	flow max rate for propylene;
	-	flow max rate for hydrogen;
	-	the ethylene : propylene : hydrogen ratios.

The actual traces for propylene and hydrogen consumed and % consumption are, like the corresponding ethylene traces, stored as values vs time.

Whilst vessels 70 into which polymer may be dumped may be of any suitable type, a preferred dumping assembly is shown in figures 6 and 7.

Referring to figure 6, the assembly includes a housing 300 which is fixed to a reactor vessel 4 (by means of fixings not shown). The housing includes an inlet 302 arranged to receive polymer from the vessel, an inlet 304 for inert gas (e.g. nitrogen) and a venting outlet 306 which communicates with the vessel 4.

The housing 300 includes a downwardly depending cylindrical outer skirt 308 and, spaced therefrom, a downwardly depending inner skirt 310. A dump vessel

assembly 312 is arranged to be releasably engaged with the housing 300 and it comprises an outer support vessel 314 and a removable insert vessel 316. The vessel 314 includes three radially extending securement pins 318 (only one of which is shown) which are arranged to be releasably engaged within respective L-shaped slots 320 (figure 7) (only one of which is shown) in a wall of the skirt 308. The pins 318 and slots 320 are disposed at 120° intervals and are arranged such that the vessel 314 can be moved upwardly within skirt 308, so that the pins 318 pass through opening 322 of the L-shaped slot; and, thereafter, by twisting the vessel 314 through a small angle, the pins pass to a retaining position 324 in the slots wherein the vessel 314 is securely retained. Disengagement of the vessel 314 is achieved by twisting the vessel in an opposite direction so that the pins can be moved downwardly and out of the slot via opening 322.

The vessel 314 includes an O-ring 326 which is arranged to sealingly engage an inwardly facing part of skirt 308 and thereby seal the inside of the assembly 312 from the outside.

The insert vessel 316 is preferably a relatively cheap, lightweight, disposable vessel and may suitably be made of aluminium. Vessel 316 is cradled within vessel 314 and is arranged to directly receive polymer from the reactor vessel. The inner skirt 310 is arranged to reduce the risk of splashing as polymer is delivered into vessel 316. The skirt 310 also includes a removable lower portion 330 which may be detached from an upper portion 332 for cleaning or replacement.

The assembly allows automation of the polymer collection. In use of the assembly, nitrogen is supplied via inlet 304 into vessel 316 so that the polymer from the reaction vessel is dumped into an inert nitrogen environment. Therefore, a robot removes assembly 312 by engaging vessel 34 and twisting it to disengage pins 318 from the slots 320. The robot then removes insert vessel 316 and places it in a storage position; replaces the removed insert vessel with a clean vessel; and re-engages the assembly 312 with housing 300. Thereafter, a subsequently prepared polymer may be delivered into the new insert vessel and the procedure repeated as required.

Thus, a multiplicity of different polymers can be prepared in the reactor vessel and dumped automatically without any operator intervention.

It will be appreciated that a single robot may be used to engage/disengage respective dump vessel assemblies when an array of apparatus for preparing polymers is used.

The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination,

except combinations where at least some of such features and/or steps are mutually exclusive.

Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

The invention is not restricted to the details of the foregoing embodiment(s). The invention extend to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

CLAIMS

1. A method of examining the effect in a chemical reaction of varying selected variables, the method comprising preparing a first product using a first set of experimental variables and preparing a second product using a second set of experimental variables, wherein data relating to said first and second sets is stored by an electronic data storage means, for example a computer.

2. A method of high-throughput screening of chemical reactions, the method comprising preparing a first product using a first set of experimental variables and preparing a second product using a second set of experimental variables, wherein data relating to said first and second sets is stored by an electronic data storage means, for example a computer.

3. A method of making a library of products, the method comprising varying experimental variables between chemical reactions in order to prepare a multiplicity of products, wherein data relating to experimental variables used for preparing each product is stored by an electronic data storage means, for example a computer.

4. A method of effecting automatically a multiplicity of chemical reactions, the method comprising preparing individual products using respective sets of experimental variables, wherein data relating to said sets is stored by an electronic data storage means, for example a computer and the preparation of said products is computer controlled.

5. A method according to any preceding claim, wherein reactions involve the use of a catalyst system and the method involves examining the effect of varying selected variables relating to said catalyst system.

6. A method according to any preceding claim, in which the effect of varying selected variables in a polymerisation reaction of one or more monomers in the presence of a catalyst system is assessed.

7. A method according to any preceding claim, wherein a reactor means is provided in which first and second products are prepared, said reactor means having a volume of at least 25 ml and less than 300 ml.

8. A method according to claim 7, wherein said reactor means includes an agitation means for agitating the content of the reactor means and means is provided for varying the extent of agitation provided by said agitation means wherein experimental variables and/or one of the variables in the first and second sets is related to the extent of agitation and said method includes the step of varying the extent of agitation between at least two chemical reactions for examining the effect of varying the agitation on the chemical reaction under consideration.

9. A method according to claim 7 or claim 8, which includes heating and/or cooling said reactor means under the control of a computer and storing data relating to the temperature in said reactor means during a chemical reaction.

10. A method according to any of claims 7 to 9, which includes supplying to the reactor means, under the control of a computer, via a first supply means, one or more components for the reaction, wherein data relating to at least one of the following is stored by said computer:

the identity of said one or more components supplied;

the timing of the supply of said component(s) in the context of the chemical reaction;

the rate at which said one or more components is supplied;

the pressure at which said one or more components is supplied;

the total amount of each of said one or more components supplied.

11. A method according to claim 10, wherein a first substance which is a reactive gas is supplied via said first supply means.

12. A method according to claim 10 or claim 11, wherein a plurality of components for the reaction are supplied via said first supply means.

13. A method according to any of claims 7 to 12, which includes assessing the amount of at least one of said components for the reaction present in the reactor means at a plurality of intervals during a reaction and adjusting the amount of said at least one said component supplied to the reactor means according to the amount assessed.

14. A method according to any of claims 7 to 13, which includes supplying to the reactor means under the control

of a computer via a second supply means one or more components for the reaction, wherein data relating to at least one of the following is stored by said computer:

the identity of said one or more components supplied;

the timing of the supply of said component(s) in the context of the chemical reaction;

the order of supply of said component(s);

the rate at which said one or more components is supplied;

the pressure at which said one or more components is supplied; and

the total amount of each of said one or more components supplied.

15. A method according to claim 14, wherein a second substance which comprises a catalyst system or a component of a catalyst system is supplied via said second supply means.

16. A method according to claim 14 or claim 15, wherein said second substance is injected into the reactor means under pressure.

17. A method according to any of claims 14 to 16, wherein a fluid reservoir means is provided upstream of the reactor means, said fluid reservoir means receiving fluid to be injected into the reactor means via said second supply means, wherein the method includes pressuring the fluid reservoir means and causing the contents thereof to be injected into the reactor means.

18. A method according to any of claims 15 to 17, wherein a catalyst system or a component of said catalyst

system supplied via said second supply means is prepared in the method and the method includes storing data relating to the preparation of said catalyst system and/or a component thereof.

19. A method according to claim 18, wherein the preparation is undertaken in an inert atmosphere.

20. A method according to any of claims 15 to 19, wherein said catalyst system or a component thereof is prepared by contacting a first catalyst component with a second catalyst component under the control of a computer and the method includes storing data relating to at least one of the following:

the identity of said first and/or second catalyst components;

the timing of the supply of said first and/or second catalyst components;

the order of the supply of said first and/or second catalyst components relative to the other components of the catalyst system; and

the amount of said first and/or second catalyst components added.

21. A method according to any preceding claim, wherein a robot is involved in the preparation of said catalyst system or a component thereof.

22. A method according to any preceding claim, wherein after termination of a chemical reaction the product produced is removed from an apparatus in which it is produced automatically under the control of a computer.

23. A method according to any preceding claim, wherein sufficient data is stored relating to chemical reactions undertaken to enable the chemical reactions to be reproduced, under computer control, to produce substantially identical products.

24. A method according to any preceding claim, wherein selection of variables for use in the reactions may be under computer control.

25. A method according to any preceding claim which involves undertaking at least five separate reactions to prepare products, wherein data relating to all of the reactions are stored by computer.

26. A method according to any preceding claim, wherein at least two substantially identical apparatuses are provided, each of which is arranged to carry out chemical reactions.

27. A method according to claim 26, wherein said at least two apparatuses are served by the same robot and are provided in, or associated with, the same inert gas filled environment.

28. A system for examining the effect of adjusting selected variables in a chemical reaction, the system comprising an apparatus which includes:

a reactor means;

a first supply means for supplying a first substance to the reactor means;

a second supply means for supplying one or more components for the chemical reaction to the reactor means;

wherein said system includes electronic data storage means, for example a computer, associated with the apparatus for storing sets of variables relating to separate reactions undertaken using the apparatus.

29. A system according to claim 28, wherein said reactor means is an autoclave, operable at a pressure up to 100 bar and a temperature up to 200°C

30. A system according to claim 28 or claim 29, which includes means for heating and means for cooling said reactor means.

31. A system according to any of claims 28 to 30, wherein means for measuring temperature is associated with the reactor means and arranged for the relay of data relating to temperature to said data storage means.

32. A system according to any of claims 28 to 31, wherein an agitator means is provided in said reactor means and is arranged such that data relating to agitation is relayed to said computer.

33. A system according to any of claims 28 to 32, wherein means for measuring the amount of fluid passing to said reactor means via said first supply means is provided and the apparatus is arranged such that data relating to said amount is relayed to said data storage means.

34. A system according to any of claims 28 to 33, wherein means is provided for analysing the level of oxygen and/or water in a fluid passing into the reactor means via said first supply means.

35. A system according to any of claims 28 to 34, wherein a receptacle is provided upstream of the reactor means wherein said receptacle includes a plurality of gas inlets and said receptacle is arranged for supply of gases from the receptacle into the reactor means via said first supply means.

36. A system according to any of claims 28 to 35, wherein said second supply means is arranged for the supply of a fluid to said reactor means and means is provided for injecting said fluid, under pressure, into said reactor means.

37. A system according to claim 36, wherein a pressurising gas is used to inject the fluid and means is provided for analysing the level of oxygen and/or water in said pressurising gas.

38. A system according to any of claims 28 to 37, which includes a catalyst preparation receptacle arranged in an inert environment and arranged for supplying catalyst to the reactor means.

39. A system according to any of claims 28 to 38, including a robot which is controlled by said computer and is arranged to transfer predetermined amounts of materials from storage positions into the apparatus.

40. A system according to any of claims 28 to 39, wherein a fluid flow path is defined between said reactor means and a collection vessel and said collection vessel is a component of a collection assembly which is releasably secured relative to the reactor means and said collection vessel is disengageable from the collection assembly.

41. A system according to claim 40, which includes a robot for releasably securing the collection assembly in position and for disengaging the collection vessel from the collection assembly.

42. A system according to any of claims 28 to 41, including a plurality of said apparatuses.

43. The use of a system according to any of claims 28 to 42, in examining the effect of adjusting selected variables in a chemical reaction.

44. The use of a system as described in any of claims 28 to 42 in high throughput screening of chemical reactions.

45. The use of a system as described in any of claims 28 to 42 in making a library of products.

46. A library of products in combination with a database incorporating data for each product, wherein said data relates to experimental variables used for preparing each product using a method according to any of claims 1 to 27 or a system according to any of claims 28 to 42.

47. The use of a system according to any of claims 28 to 42 in effecting automatically a multiplicity of chemical reactions which differ in at least one experimental variable.

FIG. 4

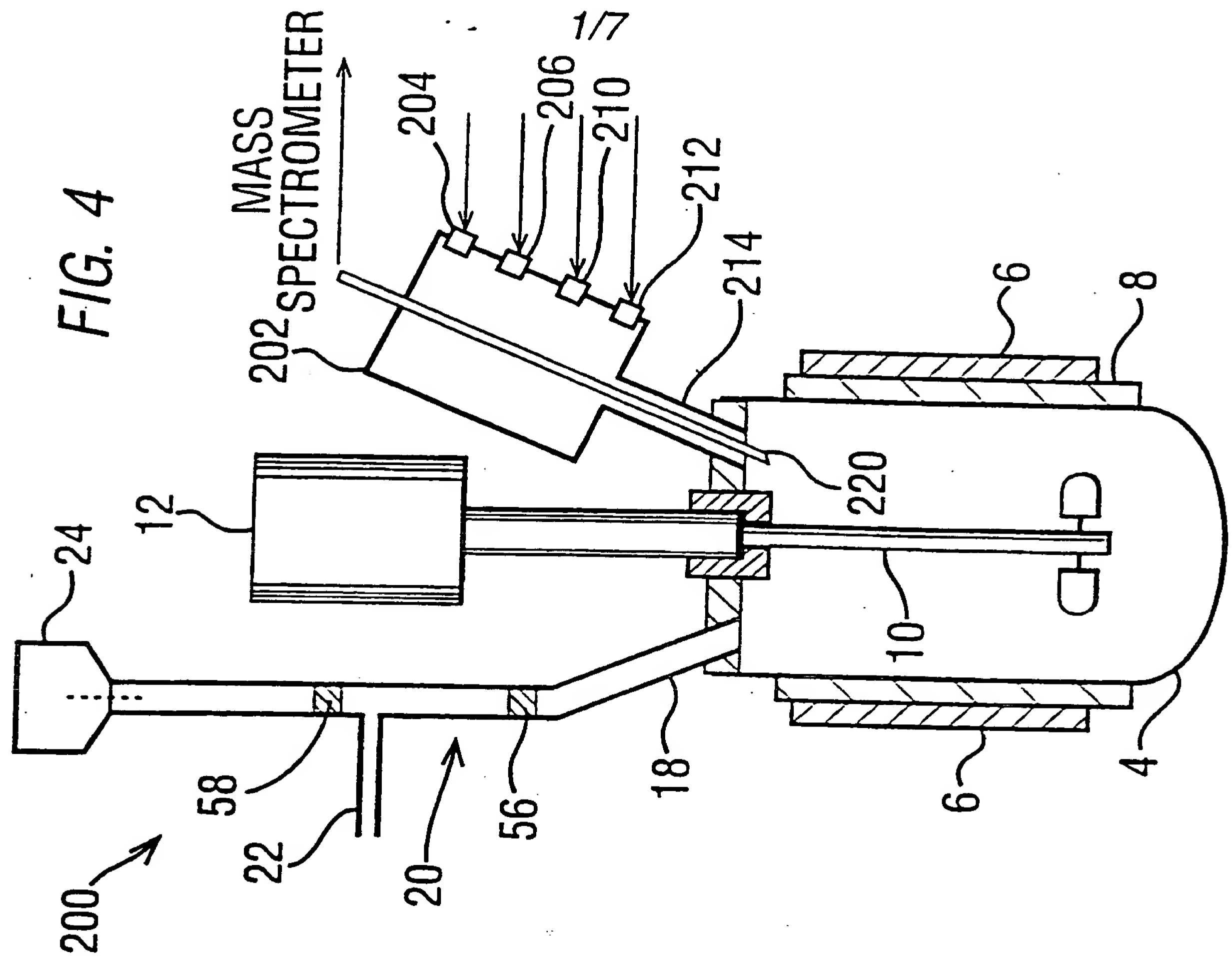
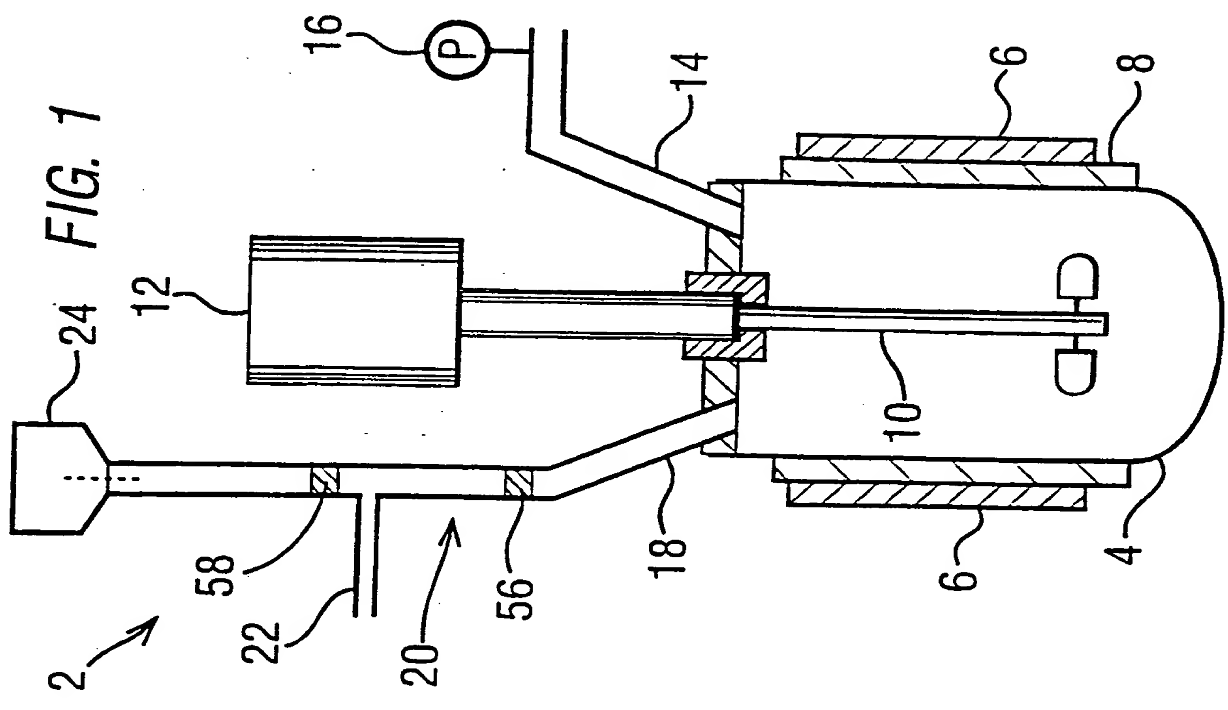

MASS
SPECTROMETER
204
206
210
212
202
214
220
24
12
10
6
8
4
18
58
56
22
20
200

FIG. 1


24
12
16
P
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6
8
10
4
18
58
56
22
20
2

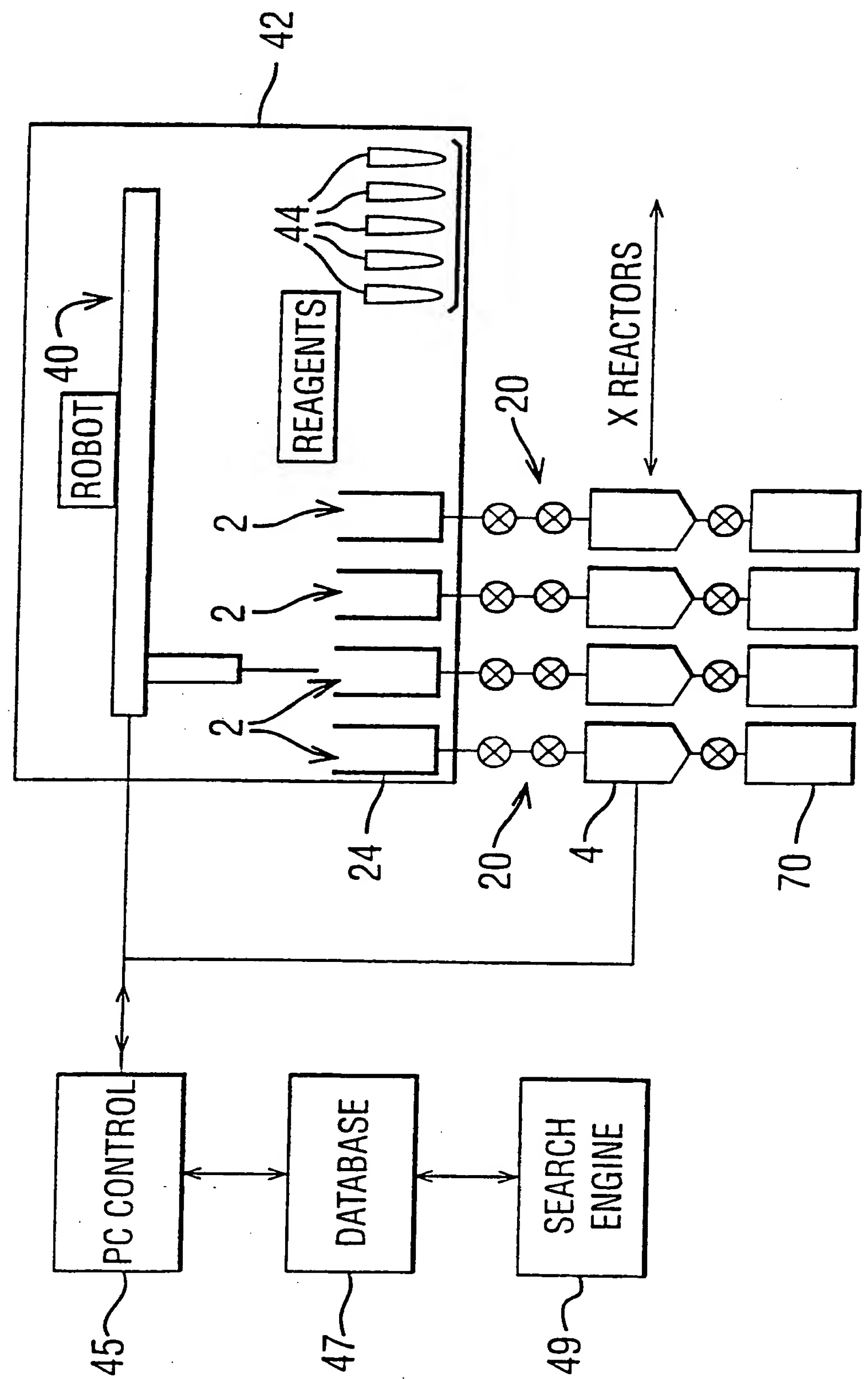

42
ROBOT
40
REAGENTS
44
X REACTORS
20
2
2
2
24
20
4
70
PC CONTROL
DATABASE
SEARCH ENGINE
45
47
49

FIG. 2

FIG. 3a

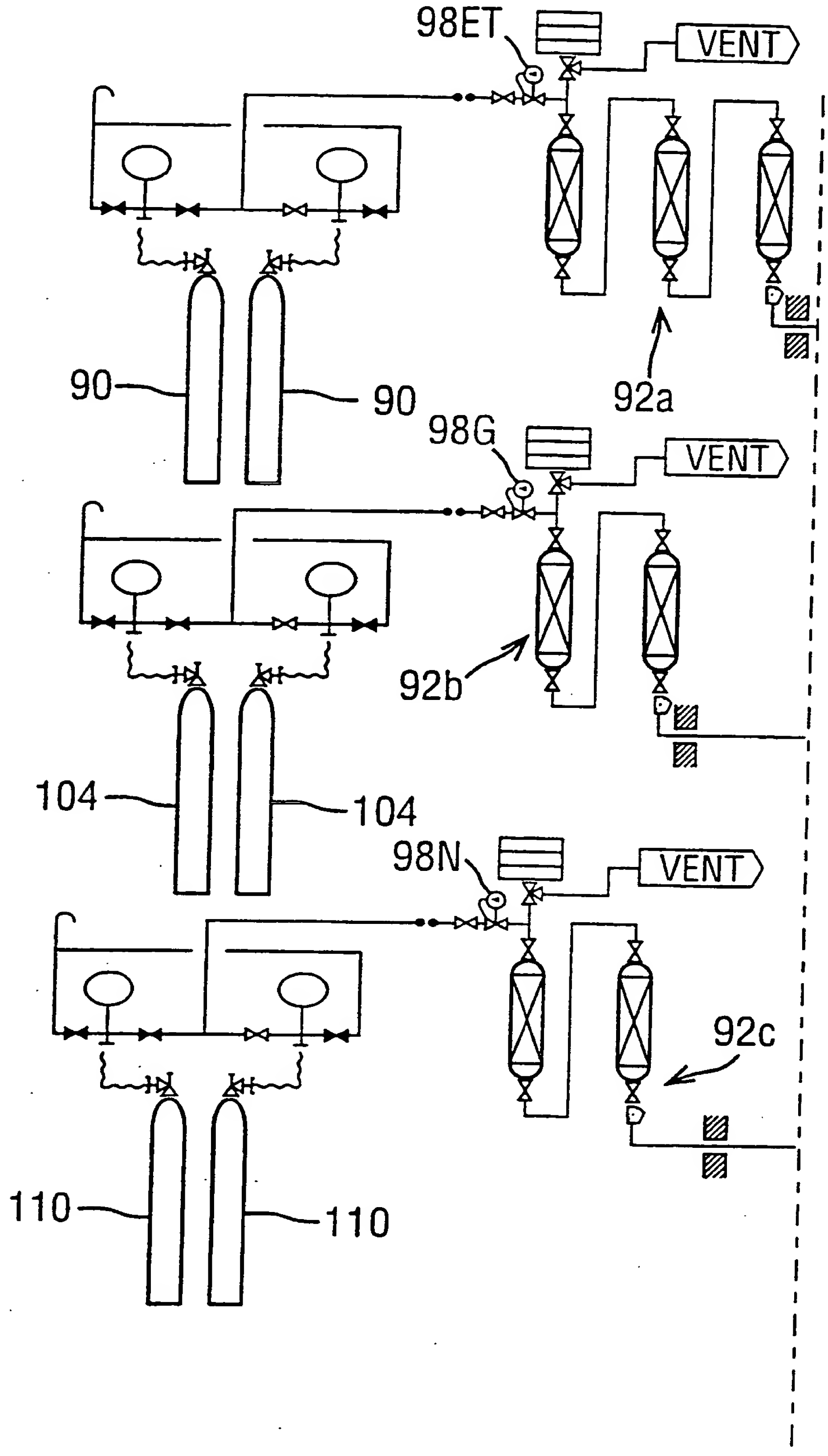


FIG. 3b

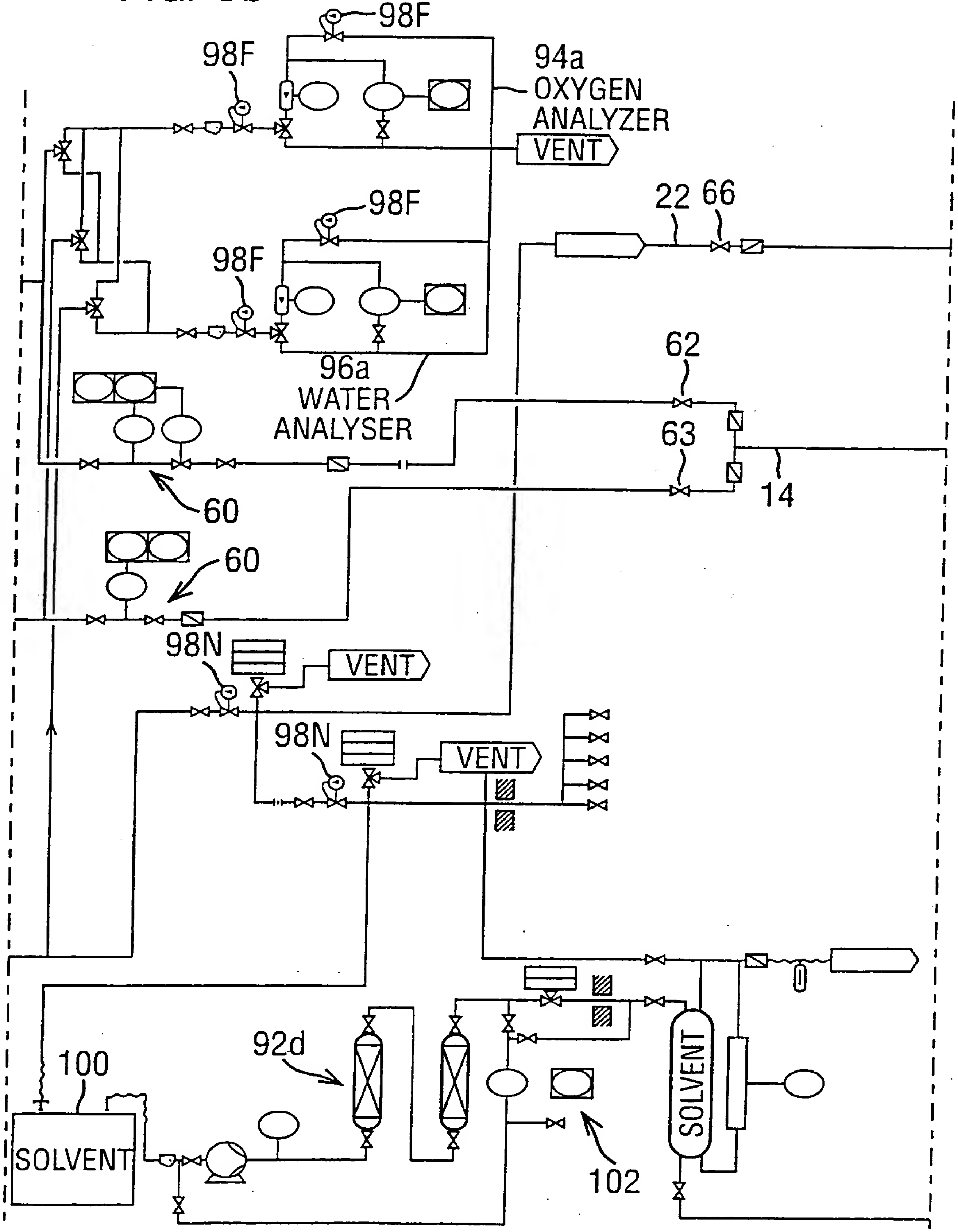

98F
98F
94a
OXYGEN
ANALYZER
VENT
98F
98F
22
66
96a
WATER
ANALYSER
62
63
14
60
60
98N
VENT
98N
VENT
92d
100
SOLVENT
SOLVENT
102

FIG. 3c

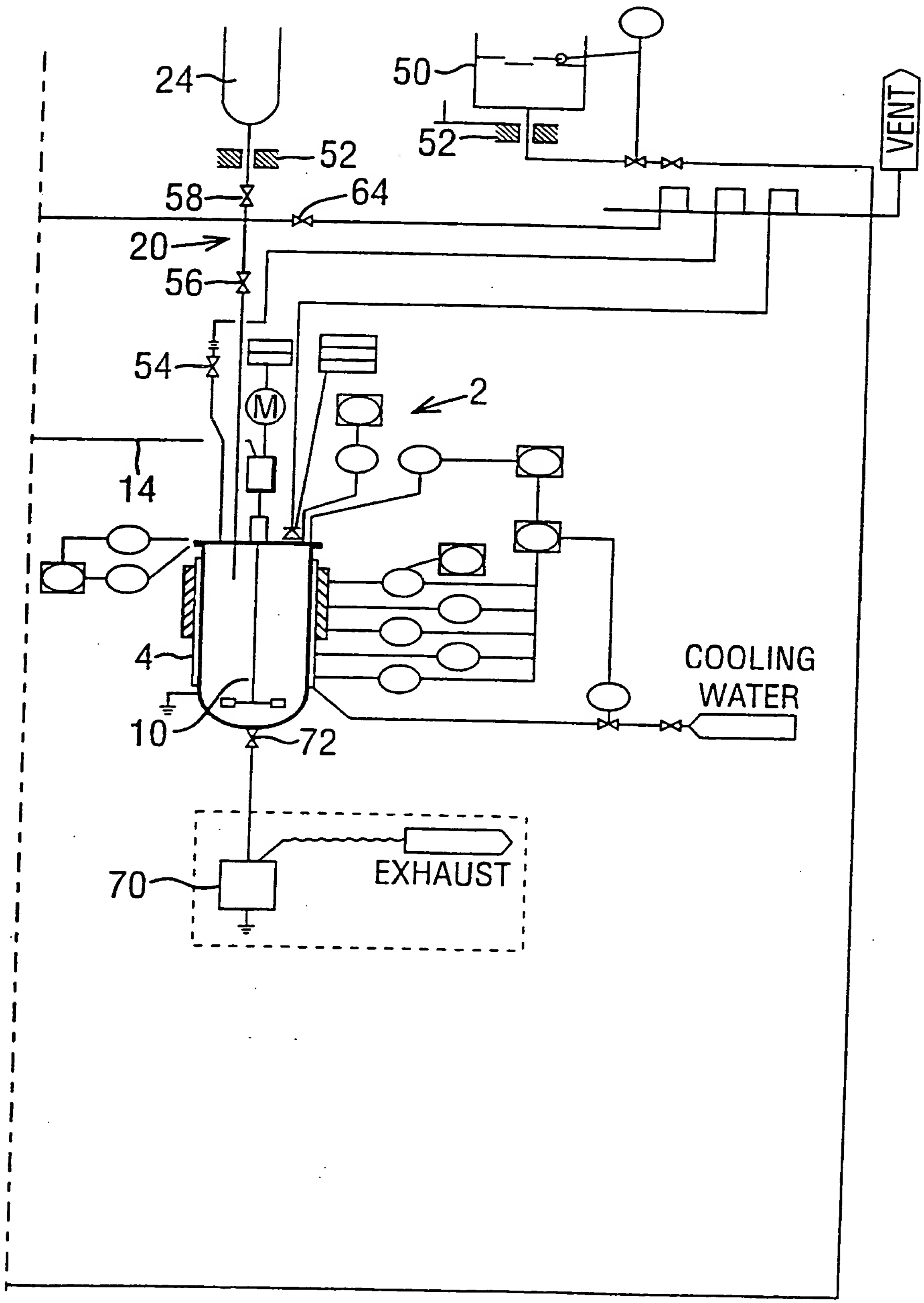

24
50
52
52
58
64
20
56
54
2
VENT
M
14
4
10
72
COOLING
WATER
70
EXHAUST

FIG. 5

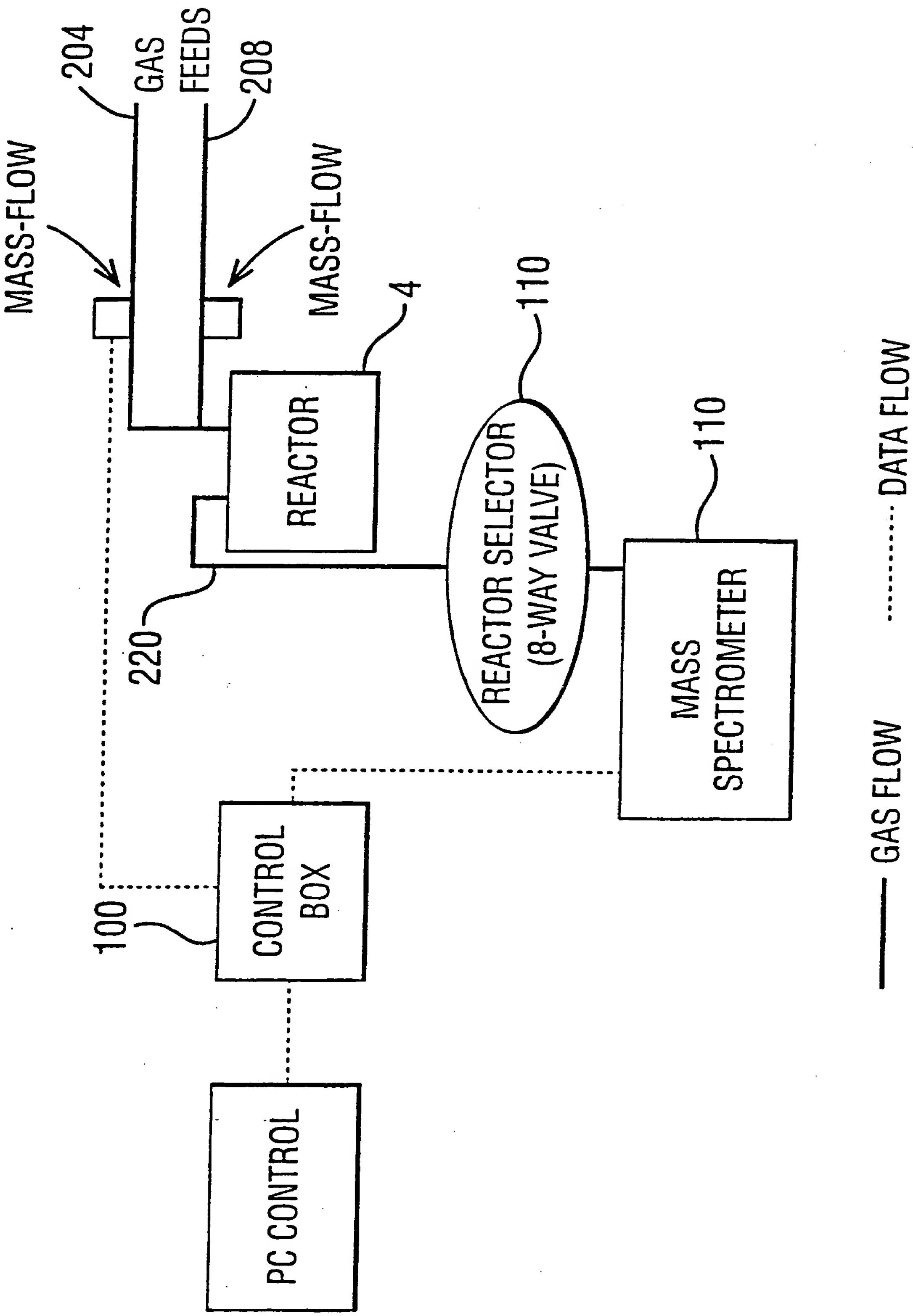

MASS-FLOW
204
GAS
FEEDS
208
MASS-FLOW
4
REACTOR
110
REACTOR SELECTOR
(8-WAY VALVE)
110
MASS
SPECTROMETER
220
100
CONTROL
BOX
PC CONTROL
GAS FLOW
DATA FLOW

FIG. 6

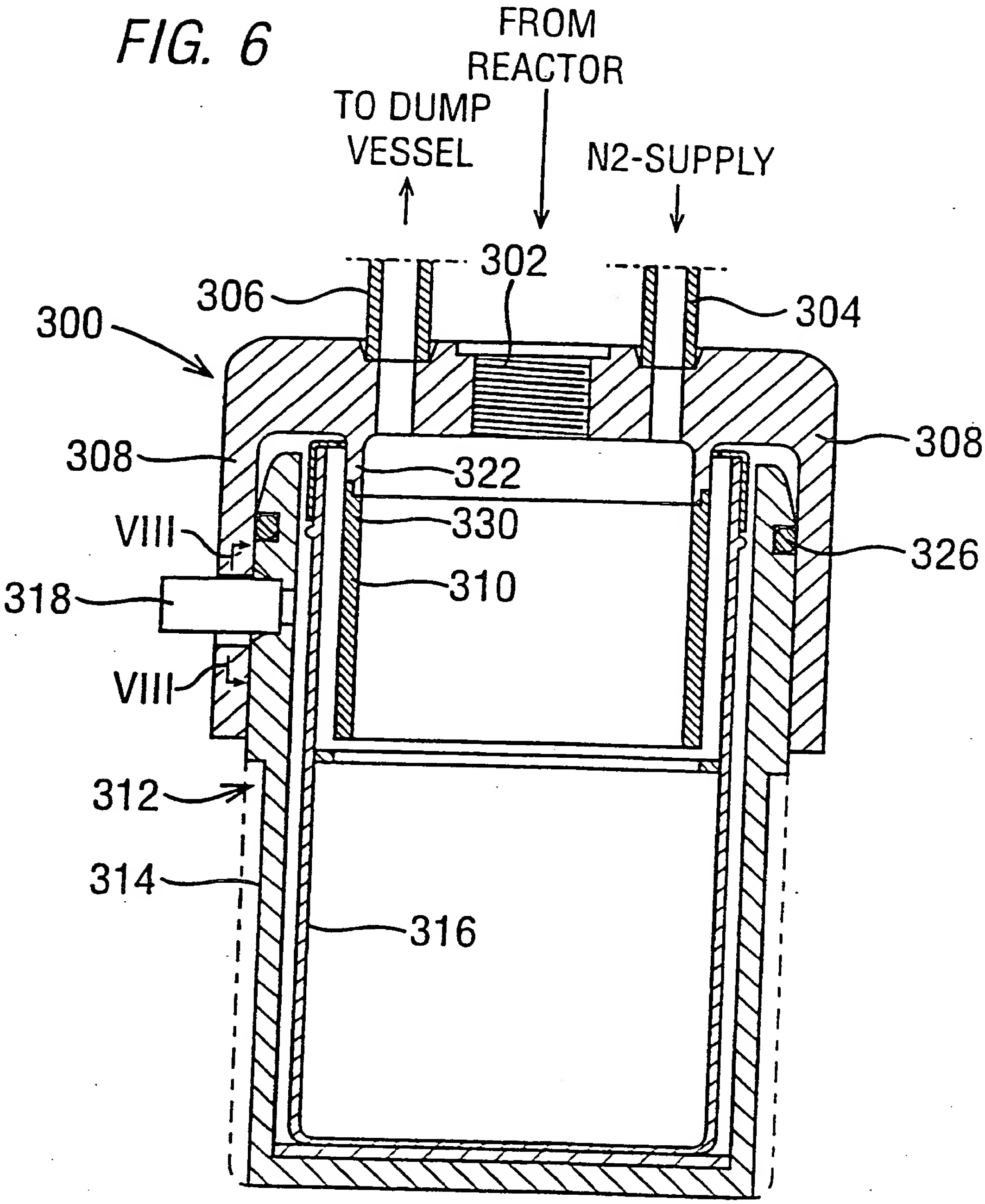
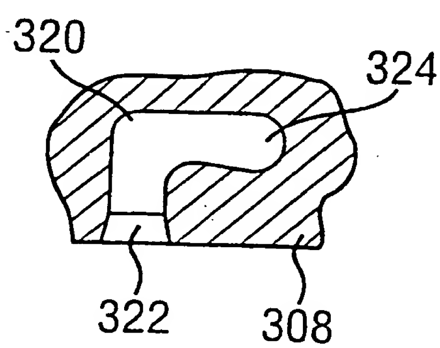

FROM
REACTOR
TO DUMP
VESSEL
N2-SUPPLY
302
306
304
300
308
308
322
330
326
VIII
310
318
VIII
312
314
316

FIG. 7


320
324
322
308

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/04370

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01J19/00 B01J3/04 B01J19/18 C08F10/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J C08F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, INSPEC, COMPENDEX

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 327 754 A (JOHNSON MATTHEY PLC) 3 February 1999 (1999-02-03)	28,30, 31,39, 42-47
A	the whole document	29, 32-38,40
X	EP 0 916 397 A (ROHM & HAAS) 19 May 1999 (1999-05-19) abstract paragraph '0012! paragraph '0014! paragraph '0016! paragraph '0054! - paragraph '0057! paragraph '0071! - paragraph '0088!; figure 8	28, 30-33, 35-38, 40,42-47

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 2001	13. 03. 2001
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Veefkind, V

1

Form PCT/ISA/210 (second sheet) (July 1992)

Inte ional Application No
PCT/GB 00/04370

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 998 995 A (BUSS RUSSEL A ET AL) 21 December 1976 (1976-12-21) column 3, line 23 -column 6, line 12; figure 1	28-31, 33,35, 36,38
X	US 3 325 453 A (DRAHOSLAV ET AL) 13 June 1967 (1967-06-13) column 3, line 26 -column 4, line 40; figure 1	28,30, 31,33, 35,36,38
X	EP 0 882 500 A (SUMITOMO CHEMICAL CO) 9 December 1998 (1998-12-09) abstract; claims 1,10-12; figures 1,3,10 column 51, line 50 -column 52, line 33 column 53, line 56 -column 54, line 35	28,30, 31,33, 36, 39-44,47
T	NEWSAM J M IN: NATO SCIENCE SERIES, VOL. 560; DEROUANE ET AL (EDS.): "Combinatorial Catalysis and High Throughput Catalyst Design and Testing: Proceedings of the NATO Advanced Study Institute on Combinatorial Catalysis and High Throughput Catalyst Design and Testing, Vilamoura, Portugal, July 11-24, 1999" December 2000 (2000-12) , KLUWER ACADEMIC PUBLISHERS , DORDRECHT, NL XP000987013 page 302, paragraph 1.2 -page 305 page 318, paragraph 6 -page 319	28-47
A	BOUSSIE T R ET AL: "Parallel Solid-Phase Synthesis, Screening, and Encoding Strategies for Olefin-Polymerization Catalysts" TETRAHEDRON,NL,ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 55, no. 39, 24 September 1999 (1999-09-24), pages 11699-11710, XP004178095 ISSN: 0040-4020 page 11702 -page 11703; figure 2	28-47

1

INTERNATIONAL SEARCH REPORT	International application No. PCT/GB 00/04370

Box I Observations wh re certain claims were found unsearchable (Continuati n of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-27
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-27

The content of claims 1-27 is such that a lack of clarity within the meaning of PCT Article 6 arises to such an extent as to render a meaningful search of these claims impossible:

The initial phase of the search revealed a very large number of documents relevant to the issue of novelty for the method claims. So many documents were retrieved that it is impossible to determine which parts of these claims may be said to define subject-matter for which protection might legitimately be sought.
In addition, the dependency and also the wording of the claims 1-27 presently on file render it difficult, if not impossible, to determine the matter for which protection is sought.

Consequently, the search has been carried out for those parts of the application which
do appear to be clear, namely claims 28-47, relating to a system for examining the effect of adjusting selected variables in a chemical reaction, the use of this system, as well as a library (insofar produced using the system).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT
Information on patent family members

Inte ional Application No
PCT/GB 00/04370

Patent document cited in search report		Publication date	Patent family member(s)		Publication dat
GB 2327754	A	03-02-1999	NONE		
EP 0916397	A	19-05-1999	JP	11236339 A	31-08-1999
US 3998995	A	21-12-1976	NONE		
US 3325453	A	13-06-1967	NONE		
EP 0882500	A	09-12-1998	JP	10132828 A	22-05-1998
			JP	11033392 A	09-02-1999
			JP	11051746 A	26-02-1999
			WO	9818549 A	07-05-1998